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Synthesis of Some New 1,3,4-Thiadiazole Derivatives and Antifungal Studies

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In the present study, some thiadiazole derivatives have been synthesized by incorporating azetidinyl and thiazolidinyl moieties at its 2-position such as 5-(*p*-methoxyphenyl)-[2-substituted benzylidenylimino] 1,3,4-thiadiazole **2(a-e)**, 5-(*p*-methoxyphenyl)-[2-(3'-chloro-2'-oxo-4'-substituted aryl-1′-azetidinyl)]-1,3,4-thiadiazole 3**(a-e)** and 5-(*p*-methoxyphenyl)-[2-(2'-substituted aryl-4'-oxo-1',3'-thiazolidin-3'-yl)]-1,3,4-thiadiazole **4(a-e)**. The structure of these compounds have been elucidated by elemental analysis (C, H, N) and IR, ^{1}H NMR, mass spectroscopic techniques. Further, these compounds were subjected to screening for antifungal activities against *Candida albican* ATCC 10231, *Aspergillus niger* ATCC 9029, *Candida tropicalis* ATCC 28775, *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019. Compound **4e** showed good antifungal activity against *C. albican* ATCC 10231 and *C. krusei* ATCC 6258 with MIC 1.562 µg/mL.

Key Words: Thiadiazole, Schiff base, Azetidinone, Thiazolidinone, Antifugal activity.

INTRODUCTION

In recent decades, problems of multi-drug resistant fungi have reached on alarming level around the world and also infections caused by those fungi pose a serious challenge to the medical community and the need for an effective therapy has led to a search for novel antifungal agents. The development of fungal resistance of existing drugs is a major problem in antifungal and necessitates continuing research into new classes of antifungal[1-3].

Among a wide variety of hetrocycles that have been explored for developing pharmaceutically important molecules. Thiadiazole have played important role in medicinal chemistry, such as antiinflammatory[4-6], anticonvulsant[7,8], antibacterial[9-11], antifungal[12-14] and many more. Also the congers of Schiff base[15,16], azetidinone[17,18] and thiazolidinone[19,20] have also been proved to exhibit promising antifungal activity. These finding prompted us to synthesize the substituted thiadiazole derivatives by the combination of azetidinone and thiazolidinone moieties in one frame may lead to compounds with interesting antifungal activity.

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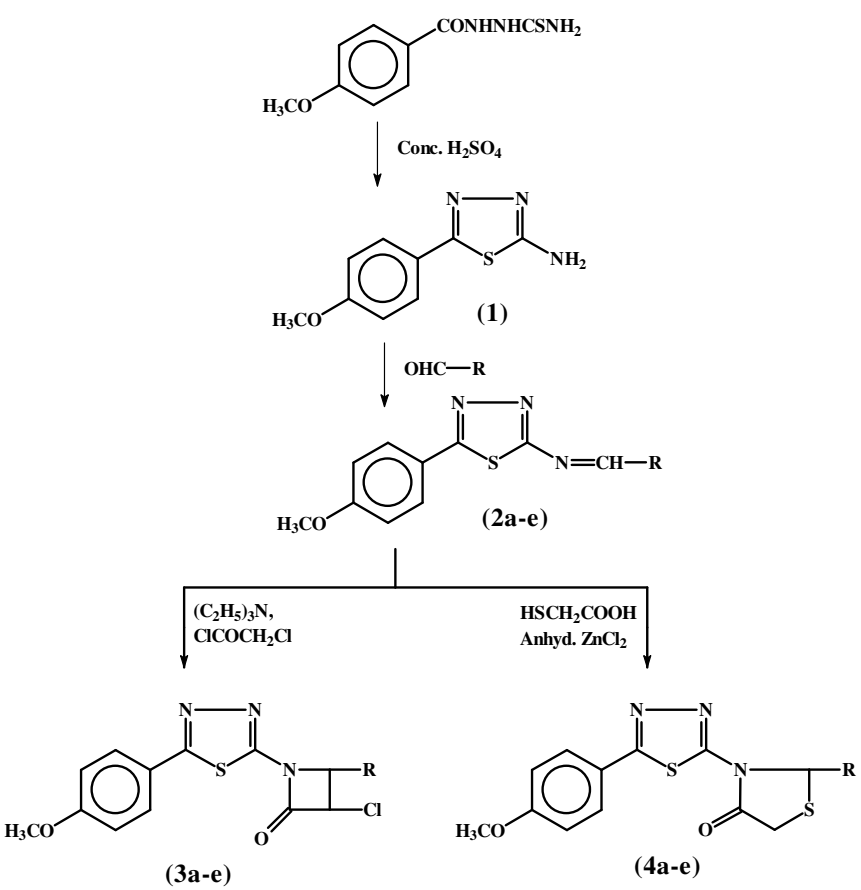
EXPERIMENTAL

The synthetic strategies adopted to obtain the target compounds are depicted in **Scheme-I**. The starting material aroyl thiosemicarbazide was treated with concentrated sulphuric acid to give 2-amino-5-(*p*-methoxyphenyl)1,3,4-thiadiazole[21] (**1**), which condensed with various aromatic aldehydes giving 5-(*p*-methoxyphenyl)-[2-substituted benzylidenylimino]1,3,4-thiadiazole **2(a-e)**. Compound **2(a-e)** were reacted further with triethyl amine/chloroacetyl chloride to yield azetidinone congeners *i.e.*, 5-(*p*-methoxyphenyl)-[2-(3'-chloro-2'-oxo-4'-substituted aryl-1′-azetidinyl)]-1,3,4-thiadiazole **3(a-e)**. On the other hand, reaction of compounds **2(a-e)** with thioglycolic acid in presence of anhydrous zinc chloride led to the formation of 5-(*p*-methoxyphenyl)-[2-(2'-substituted aryl-4'-oxo-1',3'-thiazolidin-3'-yl)]-1,3,4-thiadiazole **4(a-e)**.



R= 4-OHC_6H_4, 4-$OCH_3C_6H_4$, C_6H_5, 4-ClC_6H_4, 4-$N(CH_3)_2C_6H_4$

Scheme-I

All the reagents and solvents were generally received form commercial supplier. Reactions were done in dried glassware. Melting points were taken in open capillaries by thermonic melting point apparatus and are uncorrected. The purity of the newly synthesized compounds was checked by thin layer chromatography (TLC) on silica gel-G coated plates by using different solvent systems. Infrared (IR) spectra were determined on Bruker IFS-66 FTIR using KBr pallets and wave number (ν) was reported in cm^{-1}. The ^1H NMR spectra were taken on Jeol GSX-300 FT NMR in $CDCl_3$ or DMSO-d_6 and chemical shifts (δ) are given in ppm. Tetramethyl silane (TMS) was used as internal reference standard. Mass spectra were recorded on Spec Finnigan Mat 8230 MS. The carbon, hydrogen and nitrogen analysis were performed on Carlo Erba-1108 and the results were found within ± 0.4 % of the theoretical values.

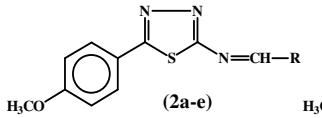
General procedure for synthesis of 2-amino-5-(*p*-methoxyphenyl)1,3,4-thiadiazole (1): A mixture of aroyl semicarbazide (0.02 mol) and concentrated sulphuric acid (20 mL) was heated on a water bath for 10 min, cooled and neutralized with ammonium hydroxide. The solid, thus separated was filtered, washed with water and recrystallized from ethanol as colourless crystal. m.p. 250 ºC, yield 69 %, Anal. for $C_9H_9N_3OS$; requires (%): C, 52.17; H, 4.34; N, 20.28. Found (%): C, 52.37; H, 4.48; N, 20.59. IR (KBr, ν_{max}, cm^{-1}1): 3265 (NH_2), 3075 (C-H aromatic), 2964 (C-H aliphatic), 1595 (C=N), 1564 ($C \doteqdot C$ of aromatic ring), 1075 (C-O-C), 1055 (N-N), 685 (C-S-C). ^1H NMR (DMSO-d_6) δ: 7.40-7.84 (m, 4H, Ar-H), 6.20 (s, 2H, NH_2, exchangeable with D_2O), 3.81 (s, 1H, OCH_3). MS: m/z 207 (M^+).

General procedure for synthesis of 5-(*p*-methoxyphenyl)-[2-substituted benzylidenylimino]1,3,4-thiadiazole 2(a-e): The equimolar amount of compound **1** (0.01 mol) and different aromatic aldehydes (0.01 mol) in ethanol (70 mL) was refluxed for 8 h in presence of few drops of glacial acetic acid. The progress and completion of the reaction were checked by TLC. After refluxing, excess of solvent was distilled off and mother liquor was dropped on crushed ice, filtered, dried and solids thus obtained were recrystallized from appropriate solvents to furnish compounds **2(a-e)**. Their characterization data are given in Table-1 and spectral data are shown in Table-2.

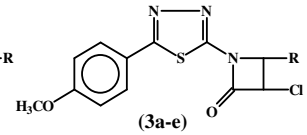
General procedure for synthesis of 5-(*p*-methoxyphenyl)-[2-(3'-chloro-2'-oxo-4'-substituted aryl-1′-azetidinyl)]-1,3,4-thiadiazole 3(a-e): To the different solutions of compounds **2(a-e)** (0.02 mol) in dry dioxane (65 mL), chloroacetyl chloride (0.04 mol) and triethyl amine (0.04 mol) were added with stirring at 0-5 ºC temperature. These different reaction mixtures were refluxed for 4-6 h and excess of solvent then distilled off. The resultant mixtures were poured onto crushed ice to afford compounds **3(a-e)**. The physical and analytical data of these compounds are given in Table-1 and spectral data are present in Table-2.

General procedure for synthesis of 5-(*p*-methoxyphenyl)-[2-(2'-substituted aryl-4'-oxo-1',3'-thiazolidin-3'-yl)]-1,3,4-thiadiazole 4(a-e): To the separate solutions of compounds **2(a-e)** (0.02 mol) in DMF (60 mL), thioglycolic acid (0.02

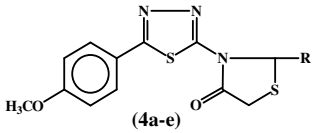
TABLE-1
CHARACTERIZATION DATA OF COMPOUNDS **2(a-e)**, **3(a-e)** AND **4(a-e)**



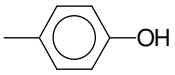
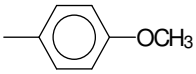
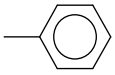
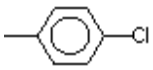
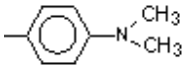
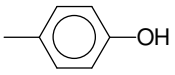
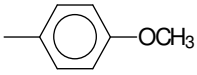
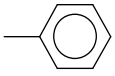
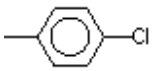
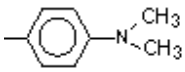
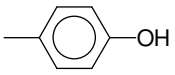
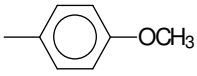
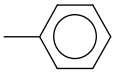
(2a-e)

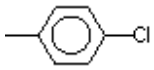
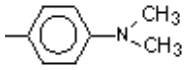


(3a-e)



(4a-e)

Comp. No.	R	m.f.	m.p. (ºC)	Yield (%)	Recryt. solvent	Elemental analysis* (%): calcd. (found.)		
						C	H	N
2a		$C_{16}H_{13}N_3O_2S$	110	65	Methanol	61.73 (61.84)	4.18 (4.07)	13.50 (13.34)
2b		$C_{17}H_{15}N_3O_2S$	118	70	Ethanol	62.76 (62.89)	4.61 (4.54)	12.92 (13.04)
2c		$C_{16}H_{13}N_3OS$	131	66	Ethanol	65.08 (64.97)	4.40 (4.53)	14.23 (14.33)
2d		$C_{16}H_{12}N_3OSCl$	125	55	Acetone	58.27 (58.47)	3.64 (3.91)	12.74 (12.66)
2e		$C_{18}H_{18}N_4OS$	118	60	Methanol	63.90 (64.06)	5.32 (5.47)	16.56 (16.71)
3a		$C_{18}H_{14}N_3O_3SCl$	138	58	Ethanol	55.74 (55.62)	3.61 (3.83)	10.83 (11.01)
3b		$C_{19}H_{16}N_3O_3SCl$	102	62	Ethanol	56.78 (56.91)	3.98 (4.13)	10.46 (10.57)
3c		$C_{18}H_{14}N_3O_2SCl$	135	55	DMF	58.14 (58.02)	3.76 (3.57)	11.30 (11.17)
3d		$C_{18}H_{13}N_3O_2SCl_2$	167	53	Benzene/ pet. ether	58.33 (58.51)	3.20 (3.43)	10.37 (10.51)
3e		$C_{20}H_{19}N_4O_2SCl$	148	55	Methanol	57.90 (58.04)	4.58 (4.45)	13.51 (13.40)
4a		$C_{18}H_{15}N_3O_3S_2$	166	40	DMF	61.18 (61.03)	4.24 (4.36)	11.89 (12.06)
4b		$C_{19}H_{17}N_3O_3S_2$	109	45	Ethanol	57.14 (57.29)	4.26 (4.37)	1052 (10.44)
4c		$C_{18}H_{15}N_3O_2S_2$	162	42	Methanol	58.53 (58.71)	4.06 (4.19)	11.38 (11.46)

4d		$C_{18}H_{14}N_3O_2S_2Cl$	128	38	Acetone	53.53 (53.67)	3.46 (3.56)	10.40 (10.31)
4e		$C_{20}H_{20}N_4O_2S_2$	125	45	Acetic acid	58.25 (58.14)	4.85 (4.73)	13.59 (13.42)

*C, H, N analysis were found within ± 0.4 % of the theoretical values.

TABLE-2
SPECTRAL DATA OF NEWLY SYNTHESIZED COMPOUNDS **2(a-e), 3(a-e)** AND **4(a-e)**

Comp. No.	IR (KBr, ν_{max}, cm^{-1})	^1H NMR δ (ppm)	MS: (m/z)
2a	3570 (O-H), 3075 (C-H aromatic), 2965 (C-H aliphatic), 1604 (C=N), 1570 (C=C of aromatic ring), 1075 (N-N), 1065 (C-O-C), 675 (C-S-C)	10.14 (s, 1H, OH, exchangeable with D_2O), 7.25-7.92 (m, 8H, Ar-H), 4.74 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.81 (s, 3H, OCH_3)	311 (M^+)
2b	3080 (C-H aromatic), 2970 (C-H aliphatic), 1595 (C=N), 1578 (C=C of aromatic ring), 1075 (N-N), 1070 (C-O-C), 678 (C-S-C)	7.29-7.71 (m, 8H, Ar-H), 4.76 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.83 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3)	325 (M^+)
2c	3064 (C-H aromatic), 2975 (C-H aliphatic), 1590 (C=N), 1585 (C=C of aromatic ring), 1080 (N-N), 1075 (C-O-C), 670 (C-S-C)	7.22-7.65 (m, 9H, Ar-H), 4.74 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.80 (s, 3H, OCH_3)	295 (M^+)
2d	3065 (C-H aromatic), 2980 (C-H aliphatic), 1610 (C=N), 1595 (C=C of aromatic ring), 1085 (N-N), 1075 (C-O-C), 675 (C-S-C)	7.26-7.82 (m, 8H, Ar-H), 4.72 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.84 (s, 3H, OCH_3)	329.5 (M^+), 331 (M + 2)
2e	3075 (C-H aromatic), 2985 (C-H aliphatic), 1588 (C=N), 1565 (C=C of aromatic ring), 1085 (N-N), (C-N-C),1060 (C-O-C), 670 (C-S-C)	7.27-7.88 (m, 8H, Ar-H), 4.75 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.79 (s, 3H, OCH_3), 2.15 (s, 6H, Ar-$N(CH_3)_2$)	338 (M^+)
3a	3570 (O-H), 3048 (C-H aromatic), 2925 (C-H aliphatic), 1740 (C=O of β-lactum ring), 1605 (C=N), 1538 (C=C of aromatic ring), 1085 (N-N), 1154 (C-N), 1075 (C-O-C), 748 (C-Cl), 645 (C-S-C)	10.14 (s, 1H, OH, exchangeable with D_2O, 7.31-7.87 (m, 8H, Ar-H), 6.56 (d, 1H, CH-Cl, *J* = 6.5 Hz), 4.71 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.81 (s, 3H, OCH_3)	387.5 (M^+), 389 (M + 2)
3b	3048 (C-H aromatic), 2925 (C-H aliphatic), 1740 (C=O of β-lactum ring), 1605 (C=N), 1538 (C=C of aromatic ring), 1085 (N-N),1154 (C-N), 1075 (C-O-C), 748 (C-Cl), 645 (C-S-C)	7.27-7.75 (m, 8H, Ar-H), 6.56 (d, 1H, CH-Cl, *J* = 6.5 Hz), 4.70 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.82 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3)	401.5 (M^+), 403.5 (M + 2)

3c	3048 (C-H aromatic), 2925 (C-H aliphatic), 1740 (C=O of β-lactum ring), 1605 (C=N), 1538 (C=C of aromatic ring), 1085 (N-N), 1154 (C-N), 1075 (C-O-C), 748 (C-Cl), 645 (C-S-C)	7.22-7.65 (m, 9H, Ar-H), 6.54 (d, 1H, CH-Cl, *J* = 6.5 Hz), 4.76 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.84 (s, 3H, OCH_3)	371.5 (M^+), 373.5 (M + 2)
3d	3048 (C-H aromatic), 2925 (C-H aliphatic), 1740 (C=O of β-lactum ring), 1605 (C=N), 1538 (C=C of aromatic ring), 1085 (N-N), 1154 (C-N), 1075 (C-O-C), 748 (C-Cl), 645 (C-S-C)	7.29-7.89 (m, 8H, Ar-H), 6.58 (d, 1H, CH-Cl, *J* = 6.5 Hz), 4.77 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.80 (s, 3H, OCH_3)	405 (M^+), 407.5 (M + 2), 409.5 (M + 4)
3e	3048 (C-H aromatic), 2925 (C-H aliphatic), 1740 (C=O of β-lactum ring), 1605 (C=N), 1538 (C=C of aromatic ring), 1085 (N-N), 1154 (C-N), 1075 (C-O-C), 748 (C-Cl), 645 (C-S-C)	7.32-7.90 (m, 8H, Ar-H), 6.57 (d, 1H, CH-Cl, *J* = 6.5 Hz) 4.75 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.79 (s, 3H, OCH_3), 2.18 (s, 6H, Ar-$N(CH_3)_2$)	414.5 (M^+), 416.5 (M + 2)
4a	3570 (O-H), 3048 (C-H aromatic), 2925 (C-H aliphatic), 1735 (C=O of thiazolidinone ring), 1605 (C=N), 1538 (C=C of aromatic ring), 1085 (N-N), 1154 (C-N), 1075 (C-O-C), 645 (C-S-C)	10.13 (s, 1H, OH, exchangeable with D_2O), 7.27-7.88 (m, 8H, Ar-H), 4.72 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.85 (s, 3H, OCH_3), 3.70 (s, 2H, CH_2 of thiazolidinone)	353 (M^+)
4b	3048 (C-H aromatic), 2925 (C-H aliphatic), 1735 (C=O of thiazolidinone ring), 1605 (C=N), 1538 (C=C of aromatic ring), 1085 (N-N),1154 (C-N), 1075 (C-O-C), 645 (C-S-C)	7.31-7.83 (m, 8H, Ar-H), 4.74 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.82 (s, 3H, OCH_3), 3.71 (s, 2H, CH_2 of thiazolidinone), 3.34 (s, 3H, OCH_3)	399 (M^+)
4c	3570 (O-H), 3048 (C-H aromatic), 2925 (C-H aliphatic), 1735 (C=O of thiazolidinone ring), 1605 (C=N), 1538 (C=C of aromatic ring), 1085 (N-N), 1154 (C-N), 1075 (C-O-C), 645 (C-S-C)	7.22-7.65 (m, 9H, Ar-H), 4.72 (d, 1H, CH-Ar, *J* = 11.0Hz), 3.81 (s, 3H, OCH_3), 3.73 (s, 2H, CH_2 of thiazolidinone)	369 (M^+)
4d	3570 (O-H), 3048 (C-H aromatic), 2925 (C-H aliphatic), 1735 (C=O of thiazolidinone ring), 1605 (C=N), 1538 (C=C of aromatic ring), 1085 (N-N), 1154 (C-N), 1075 (C-O-C), 748 (C-Cl), 645 (C-S-C)	7.28-7.75 (m, 8H, Ar-H), 4.75 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.82 (s, 3H, OCH_3), 3.69 (s, 2H, CH_2 of thiazolidinone)	403.5 (M^+), 405.5 (M + 2)
4e	3570 (O-H), 3048 (C-H aromatic), 2925 (C-H aliphatic), 1735 (C=O of thiazolidinone ring), 1605 (C=N), 1538 (C=C of aromatic ring), 1085 (N-N), 1154 (C-N), 1075 (C-O-C), 645 (C-S-C)	7.29-7.86 (m, 8H, Ar-H), 4.76 (d, 1H, CH-Ar, *J* = 11.0 Hz), 3.81 (s, 3H, OCH_3), 3.70 (s, 2H, CH_2 of thiazolidinone), 2.15 (s, 6H, Ar-$N(CH_3)_2$)	412 (M^+)

mL) and anhydrous $ZnCl_2$ (0.02 mol) were added. These reaction mixtures were heated under reflex for 6 h. After completion of reaction, excess of solvent was distilled off, then cooled and poured onto crushed ice. Solids thus separated out were crystallized from appropriate solvent to furnish compounds **4(a-e)**. The physical and analytical data are shown in Table-1 and spectral data are shown in Table-2.

Pharmacological evaluation: The compounds **2(a-e), 3(a-e), 4(a-e)** and standard drug, flucanozole, have been evaluated for antifungal activity. In order to determine the antifungal activity of proposed compounds, inhibitory zone diameter and minimal inhibitory concentration were tested against *Candida albican* ATCC 10231, *Aspergillus niger* ATCC 9029, *Candida tropicalis* ATCC 28775, *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019.

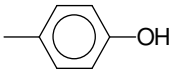
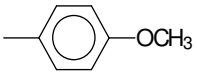
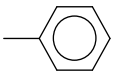
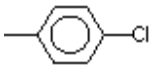
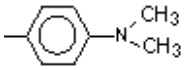
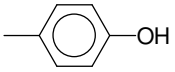
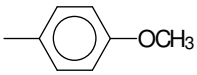
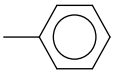
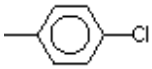
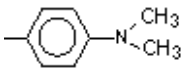
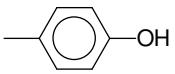
Antifungal activity: Newly synthesized compounds **2(a-e), 3(a-e), 4(a-e)** and standard drug, fluconazole were evaluated for antifungal by employing standard agar disc diffusion method[22]. The following strains of fungus have been used in this study: *Candida albican* ATCC 10231, *Aspergillus niger* ATCC 9029, *Candida tropicalis* ATCC 28775, *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019. All cultures were maintained on SDA and incubated at 30 ºC. To prepare homogeneous suspensions of above fungi for disc assays, they were grown in sabouraud broth centrifuged to collect the pellet and buffered saline. The fungal pellet was homogenized in a sterile hand held homogenizer. This suspension was then plated onto SDA using fungal spreader to obtain an even growth field. Sterile 6 mm Whatmann filter paper impregnated with 200 µg/mL concentration of various test compounds and standard drug, fluconazole. These discs were then placed in the centre of each quadrant of an SDA plate. Each plate had one control disc impregnated with DMSO. The plates were incubated at 30 ºC. After 48 h, the plates were removed.

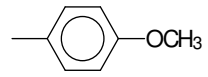
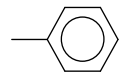
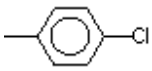
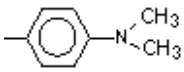
Minimal inhibitory concentration (MIC): The antifungal activity was assayed *in vitro* by the two fold broth dilution[23] against *Candida albican* ATCC 10231, *Aspergillus niger* ATCC 9029, *Candida tropicalis* ATCC 28775, *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019. The minimal inhibitory concentrations (MIC, µg/mL) were defined as the lowest concentrations of compound that completely inhibited the growth of each strain. All compounds, dissolved in dimethyl sulfoxide, were added to culture media. Mueller Hinton Broth for bacteria and sabouraud liquid medium for fungi to obtain final concentrations ranging from 200.000-1.592 µg/mL. The amount of dimethyl sulfoxide never exceeded 1 % v/v. Inocula consisted of 1×10^3 fungi/mL. The MICs were read after incubation at 30 °C for 48 h (fungi). Media and media with 1 % v/v dimethyl sulfoxide were employed as growth controls. fluconazole were used as reference antifungal drugs. To detect the type of antifungal activity, subcultures were performed by transferring 100 µL of each mixture remaining clear in 1 mL of fresh medium. The minimal fungicidal concentrations (MFC, µg/mL) were read after incubation at 37 °C for 24 h and at 30 °C for 48 h.

RESULTS AND DISCUSSION

The antifungal screening showed that all the tested compounds **2(a-e), 3(a-e)** and **4(a-e)** showed moderate to good inhibitory growth against *Candida albican* ATCC 10231, *Aspergillus niger* ATCC 9029, *Candida tropicalis* ATCC 28775, *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019 at 200 µg/mL concentration. Results of inhibitory zone diameter (Table-3) and minimal inhibitory concentration (Table-4) showed varying degree of antifungal activity of tested compounds.

TABLE-3
INHIBITORY ZONE DIAMETER (mm) OF SYNTHESIZED COMPOUNDS **2(a-e), 3(a-e)** AND **4(a-e)** AGAINST TESTED FUNGAL STRAINS

Comp. No.	R	Antifungal activity* diameter of the inhibition zone (mm)				
		C. albican ATCC 10231	*A. niger* ATCC 9029	*C. tropicalis* ATCC 28775	*C. krusei* ATCC 6258	*C. parapsilosis* ATCC 22019
2a		13	14	11	–	–
2b		15	20	18	07	14
2c		–	15	10	–	10
2d		11	10	–	13	16
2e		09	21	17	16	19
3a		21	24	16	17	22
3b		27	31	26	22	25
3c		–	19	14	–	19
3d		17	21	20	15	21
3e		25	29	24	19	24
4a		–	27	21	19	25

4b		29	30	25	20	26
4c		19	21	17	14	–
4d		23	24	20	–	21
4e		31	33	27	23	28
Control**		0	0	0	0	0
Flucanozole		26	28	24	21	26

*Concentration was 200 μg/mL, **DMSO.

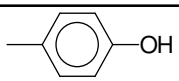
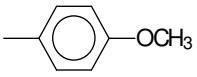
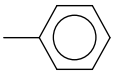
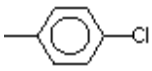
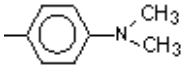
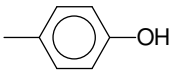
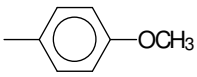
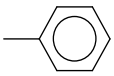
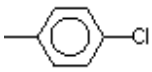
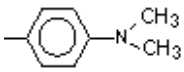
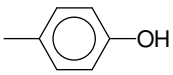
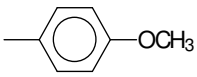
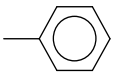
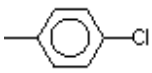
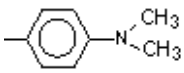
Compound **3b** exhibited higher activity against *Aspergillus niger* ATCC 9029 and *Candida tropicalis* ATCC 28775 than standard drug with MIC 6.25 μg/mL. Compound **4b** showed more potent against *Candida albican* ATCC 10231 and *Aspergillus niger* ATCC 9029 than standard drug with MIC 3.125 and 6.25 μg/mL, respecively. Among these compounds tested, compounds **4e** was found to be more potent antifungal agents against all the fungal strains as compared to reference drug and its MIC were determined to be 1.592-6.250 μg/mL. Further, many compounds (**3b, 3e, 4a** and **4b**) displayed antifungal property equipotent to the reference drug. Rest compounds of this series showed moderate activity as compared to standard drug.

The antifungal result revealed that the conversion of compounds **2(a-e)** into their corresponding azetidinone congeners **3(a-e)** and thiazolidinone congeners **4(a-e)** increases the inhibition action against the growth of different fungal strains. However, compound **4(a-e)** bearing thiazolidinone ring exhibited better antifungal activity as compared to β-lactam ring bearing compounds **3(a-e)**. Furthermore, among azetidinone and thiazolidinone congeners, compounds having *p*-methoxyphenyl group **(3b, 4b)** and *p*-amino dimethylphenyl **(4e)** showed better activity in their respective groups against different fungal strains.

Conclusion

Compound **4e**: 5-(*p*-methoxyphenyl)-[2-(2'-(*p*-aminodimethylphenyl)-4'-oxo-1',3'-thiazolidin-3'-yl)]-1,3,4-thiadiazole was found to be the most active compound, as it exhibited better antifungal activity as compared to reference drugs. At the end, it may be concluded that the presence of *p*-methoxyphenyl and *p*-amino dimethylphenyl as a substituent elicits a remarkable increase in biological profile. Cyclization of substituted Schiff bases into their corresponding azetidinone and thiazolidinone congeners enhances the antifungal activity. Compounds having thiazolidinone ring displayed better biological results than those containing azetidinone moiety.

TABLE-4
MINIMUM INHIBITORY CONCENTRATION (MIC) SYNTHESIZED COMPOUNDS **2(a-e), 3(a-e)** AND **4(a-e)** AGAINST TESTED FUNGAL STRAINS

Comp. No.	R	Minimum inhibitory concentration (MIC) (µg/mL)				
		C. albican ATCC 10231	*A. niger* ATCC 9029	*C. tropicalis* ATCC 28775	*C. krusei* ATCC 6258	*C. parapsilosis* ATCC 22019
2a		100	>125	>125	–	–
2b		50	50	50	100	100
2c		–	100	>125	–	100
2d		100	>125	–	25	50
2e		100	50	50	12.5	50
3a		12.5	25	100	6.25	25
3b		6.25	6.25	6.25	3.125	12.5
3c		–	100	100	–	50
3d		25	50	25	12.5	25
3e		6.25	12.5	12.5	3.125	25
4a		–	12.5	25	12.5	12.5
4b		3.125	6.25	12.5	3.125	12.5
4c		25	50	50	25	–
4d		12.5	25	25	–	25
4e		1.562	3.125	6.25	1.562	6.25
Flucanazole		6.25	12.5	12.5	3.125	12.5

–Denotes no activity was observed

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